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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,238	09/25/2003	Rudi Rossau	12546.2USC4	8516

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,238	ROSSAU ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-86* is/are pending in the application.

4a) Of the above claim(s) *73 and 74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-72 and 75-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 07/965,394.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12-8-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 41-72 and 75-86 in the reply filed on June 16, 2006 is acknowledged.

Priority

2. As set forth on the first line of the specification, the present application claims priority under 35 U.S.C. 120 to as a continuation of U.S. application 09/863,086, which is a continuation of 09/312,520, which is a continuation of 08/635,761, which is a continuation of 08/412,614, which is a continuation of 07/965,394, filed December 17, 1992. This application also claims priority under 35 U.S.C. 119 to UK 90 401 054.3, filed April 18, 1990. However, the UK document was filed more than one year prior to the filing of the '394 application. The claim to priority does not include a statement that application 07/965,394 is a continuation of PCT/EP91/00743, filed April 18, 1991 (see the Oath/Declaration filed September 25, 2003). Accordingly, the first line of the specification should be amended to recite that application 07/965,394 is a continuation of PCT/EP91/00743, filed April 18, 1991

Objections to the Claims

3. Claims 50-62 and 67-69 are objected to over the following informalities:

Claims 50-62 are objected to over the recitation of "**a** complementary nucleic acid sequence**s**" (see claim 50) whereas this phrase should read either "complementary nucleic acid sequences" or "a complementary nucleic acid sequence."

. Claims 67-69 are objected to over the recitation of "of **at** a non-viral organism" (see claim 67). This phrase should be amended to read "of a non-viral organism."

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-72 and 75-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

> Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

Claims 41-72 and 75-86 are inclusive of nucleic acids comprising sequences of a spacer region between the large subunit and small subunit rRNA of any non-viral organism, or the large subunit and the 5S subunit rRNA of any non-viral organism, or an RNA form thereof. The genus of non-viral organisms is significantly extensive, including millions of highly diverse organisms, which differ substantially with respect to their nucleotide sequences. As detailed below, the claims do not define the nucleic acids in terms of their overall length, structure (e.g., nucleotide sequence), their specific source (i.e., a particular organism) or their specific function.

In particular, claims 41-42, 44 and 46 are drawn to nucleic acid molecules which comprise a sequence of a length of about the maximum number of nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. These claims define only the length of the nucleotide sequence comprised by the nucleic acid molecule, but do not define the sequence itself. In view of the comprising language, the nucleic acid molecule may contain additional 5' and 3' flanking nucleotides. Accordingly, the claimed nucleic acid molecules are not defined in terms of any structural or functional properties. Further, the phrase "RNA forms thereof" is not defined in the specification and has been interpreted as including any RNA form of a nucleic acid sequence, wherein the RNA form may include any number and identity of nucleotide substitutions, and may include pre-processed versions of an RNA molecule or post-processed forms of an RNA molecule.

Claims 43, 45, 47-49 are drawn to nucleic acid molecules comprising any 15 to 100 contiguous nucleotides obtained from a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Since the claims recite the term "comprising", the claims may include nucleic acids of any length (e.g., full length chromosomes). While the claims recite that the nucleic acid comprising an oligonucleotides that "is able to hybridize specifically" to a target that does not include tRNA genes, this recitation is not considered to further define the structure of the nucleic acid molecule. The claims do not set forth any particular hybridization conditions. Also, while an oligonucleotide may hybridize to a sequence that lacks a tRNA gene sequence, this does not mean that the nucleic acid

molecule comprising the oligonucleotides does not contain sequences complementary to a tRNA gene. Further, the phrase "hybridize specifically to a target" is not defined in the specification. For instance, this phrase has not been defined in the specification to be limited to oligonucleotides which hybridize to only one target (i.e., the target to which it is 100% complementary) and do not cross-hybridize to any other target, such as targets which share 99% complementarity. In the absence of a clear definition for this phrase, this phrase is not considered to further limit the structure or function of the oligonucleotides or the nucleic acid molecule comprising the oligonucleotides.

Claims 50-62 are drawn to methods which require the use of a probe comprising any 15 to 100 contiguous nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Again, since the claims recite the term "comprising", and thereby the claims encompass the use of nucleic acid probes of any length (e.g., full length chromosomes). Also, the spacer region is not defined in terms of any particular nucleotide sequence or length. The recitation in the claims that the probe forms a hybrid with a complementary nucleic acid sequence does not serve to further limit the structure or function of the claims since the claims do not recite any particular conditions of hybridization, do not recite the degree of complementarity shared between the probe and the target sequences and do not define the target sequences.

Claims 63-66 broadly encompass any method of using a target nucleic acid wherein the target nucleic acid has a sequence of a maximum number of nucleotides of a spacer region. The claims define the length of a target sequence, but do not define

the identity of the nucleotides in the target sequence (i.e., there is no requirement that the target sequence comprises spacer sequences, it must only have the number of nucleotides of a spacer sequence). Further, the claims do not state how the target is used to detect a non-viral organism and do not define any probes or primers which would be used to detect a target region.

Claims 67-69 are drawn to methods for detecting a non-viral organism by amplifying nucleic acids using primers that comprise any 15 to 100 nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Claims 75-86 are drawn to kits comprising primers and probes of the same scope. Again, since the claims recite the term "comprising", and the claims encompass nucleic acid primers and probes of any length. Also, the spacer region is not defined in terms of any particular nucleotide sequence or length. The claims also define the oligonucleotide in terms of its ability to hybridize specifically to a target. However, the specification does not provide a definition for the phrase "specifically hybridize" and there is no fixed definition in the art for this phrase. It is unclear from the teachings in the specification as to which nucleic acids the oligonucleotides hybridize with and which nucleic acids the oligonucleotides do not hybridize with. Absence such a teaching, the language "specifically hybridizes" has been interpreted broadly and is not considered to impart any particular structural or functional limitations onto the oligonucleotides.

Claims 70-72 are drawn to methods which require the use of primers "derived" from a spacer region between the large subunit and small subunit rRNA, the large

subunit and the 5S subunit rRNA, or an RNA form thereof. The specification teaches that "rRNA gene spacer region derived" sequences refers to any probe that hybridizes to a spacer region. The conditions and specificity of hybridization are not defined. Accordingly, such sequences are given their broadest, most reasonable interpretation as encompassing spacer sequences which may include any number of nucleotide substitutions, deletions or additions. Thereby, the claimed primers are not considered to be defined in terms of a particular structure or length.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses the spacer sequences between the 16S rRNA and 23S rRNA of 10 procaryotic microorganisms. The specification also exemplifies oligonucleotides from these spacer regions which can be used to distinguish between different species of the stated prokaryotic microorganism. For instance, the specification teaches oligonucleotides that can be used in a hybridization assay to distinguish between nucleic acids of *Neisseria meningitides* and nucleic acids of *Neisseria gonorrhoeae*.

Accordingly, the written description requirement has been met for nucleic acid probes and primers consisting of a sequence of a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, wherein the sequence comprises about 15 to about 100 contiguous nucleotides from a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, and wherein the probes or primers are species specific and do not includes sequences of a

tRNA gene.

However, the claims as very broadly written encompass nucleic acids, probes and primers obtained from any eukaryotic microorganism. Yet, the specification does not teach a single nucleic acid, probe or primer containing spacer sequences from a eukaryotic microorganism. Also, the specification does not exemplify any probes or primers containing sequences from regions other than the transcribed spacer region between the 16S and 23S rRNAs, as are included by the claims as broadly written to include any nucleic acid sequence (i.e., the claims which define the number of nucleotides, but not the identity of the nucleotides; those aspects of the claims directed to "RNA forms"; and claims directed to nucleic acids "derived" from a spacer region). Additionally, the specification teaches only nucleic acids, probes and primers which can be used to detect and/or distinguish between different species of prokaryotic microorganisms. The specification does not exemplify any nucleic acids having any other functional attributes.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, while the art teaches genomic sequences from other organisms, the specification provides no guidance as to how one may use particular sequences within the genomic sequences to obtain primers or probes for the detection of particular target non-viral organisms. Given the substantial differences in the structure nucleic acid molecules from diverse organisms, the structure

and function of one molecule does not provide guidance as to the structure and function of other molecules. Therefore, the description of 10 spacer regions from prokaryotic microorganisms is not representative of the broadly claimed genus of any nucleic acid probe or primer comprising a spacer region from any non-viral organism. A general statement in the specification of a desire to obtain spacer sequences and to use spacer sequences as probes or primers to detect organisms is not equivalent to providing a clear and complete description of specific sequences which fall within the claimed genus of nucleic acids. Accordingly, the specification does not disclose a representative number of species in terms of a specific structure or in terms of any other relevant, identifying characteristics.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Further, Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. Additionally, *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now

claimed".

In the instant application, because of the limited amount of structural information or the complete absence of structural information regarding the claimed nucleic acid molecules, primers and probes, one of skill in the art cannot envision the detailed chemical structure of these nucleic acids, regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that analysis of such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acid sequences is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the broadly claimed genus of nucleic acid molecules, primers and probes, methods for using said nucleic acid molecules, primers and probes or kits containing said nucleic acid molecules, primers and probes. Accordingly, it is concluded that the specification does not provide adequate written description for the claims as they are broadly written.

5. Claim 81 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not appear to provide support for the concept of immobilizing a primer to a solid support as is required by newly added claim

81. While the specification teaches the immobilization of probes to a solid support, wherein the probes are to be used in a probe hybridization assay, the specification does not appear to teach the concept of immobilizing primers onto a solid support.

6. Claims 41-72 and 75-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) isolated nucleic acid probes and primers consisting of a sequence of a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, wherein the sequence comprises about 15 to about 100 contiguous nucleotides from a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, and wherein the probes or primers are species specific and do not includes sequences of a tRNA gene, (ii) kits containing said probes or primers, and (iii) methods for detecting a prokaryotic microorganism using said probes or primers, does not reasonably provide enablement for nucleic acids, probes or primers comprising any eukaryotic or prokaryotic spacer region consisting of or derived from any region between a large subunit and small subunit of an rRNA gene or any other molecule or between the large subunit and 5S subunit of an rRNA gene, or comprising a sequence of any identity having the maximum number of nucleotides of a spacer region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the

predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 41-72 and 75-86 are inclusive of nucleic acids comprising sequences of a spacer region between the large subunit and small subunit rRNA of any non-viral organism, or the large subunit and the 5S subunit rRNA of any non-viral organism, or an RNA form thereof. The genus of non-viral organisms is significantly extensive, including millions of highly diverse organisms, which differ substantially with respect to their nucleotide sequences. As detailed below, the claims do not define the nucleic acids in terms of their overall length, structure (e.g., nucleotide sequence), their specific source (i.e., a particular organism) or their specific function.

In particular, claims 41-42, 44 and 46 are drawn to nucleic acid molecules which comprise a sequence of a length of about the maximum number of nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. These claims define only the length of the nucleotide sequence comprised by the nucleic acid molecule, but do not define the sequence itself. In view of the comprising language, the nucleic acid molecule may contain additional 5' and 3' flanking nucleotides. Accordingly, the claimed nucleic acid molecules are not defined in terms of any structural or functional properties. Further, the phrase "RNA forms thereof" is not defined in the specification and has been interpreted as including any RNA form of a nucleic acid sequence, wherein the RNA form may

include any number and identity of nucleotide substitutions, and may include pre-processed versions of an RNA molecule or post-processed forms of an RNA molecule.

Claims 43, 45, 47-49 are drawn to nucleic acid molecules comprising any 15 to 100 contiguous nucleotides obtained from a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Since the claims recite the term "comprising", the claims may include nucleic acids of any length (e.g., full length chromosomes). While the claims recite that the nucleic acid comprising an oligonucleotides that "is able to hybridize specifically" to a target that does not include tRNA genes, this recitation is not considered to further define the structure of the nucleic acid molecule. The claims do not set forth any particular hybridization conditions. Also, while an oligonucleotide may hybridize to a sequence that lacks a tRNA gene sequence, this does not mean that the nucleic acid molecule comprising the oligonucleotides does not contain sequences complementary to a tRNA gene. Further, the phrase "hybridize specifically to a target" is not defined in the specification. For instance, this phrase has not been defined in the specification to be limited to oligonucleotides which hybridize to only one target (i.e., the target to which it is 100% complementary) and do not cross-hybridize to any other target, such as targets which share 99% complementarity. In the absence of a clear definition for this phrase, this phrase is not considered to further limit the structure or function of the oligonucleotides or the nucleic acid molecule comprising the oligonucleotides.

Claims 50-62 are drawn to methods which require the use of a probe comprising any 15 to 100 contiguous nucleotides of a spacer region between the large subunit and

small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Again, since the claims recite the term "comprising", and thereby the claims encompass the use of nucleic acid probes of any length (e.g., full length chromosomes). Also, the spacer region is not defined in terms of any particular nucleotide sequence or length. The recitation in the claims that the probe forms a hybrid with a complementary nucleic acid sequence does not serve to further limit the structure or function of the claims since the claims do not recite any particular conditions of hybridization, do not recite the degree of complementarity shared between the probe and the target sequences and do not define the target sequences.

Claims 63-66 broadly encompass any method of using a target nucleic acid wherein the target nucleic acid has a sequence of a maximum number of nucleotides of a spacer region. The claims define the length of a target sequence, but do not define the identity of the nucleotides in the target sequence (i.e., there is no requirement that the target sequence comprises spacer sequences, it must only have the number of nucleotides of a spacer sequence). Further, the claims do not state how the target is used to detect a non-viral organism and do not define any probes or primers which would be used to detect a target region.

Claims 67-69 are drawn to methods for detecting a non-viral organism by amplifying nucleic acids using primers that comprise any 15 to 100 nucleotides of a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. Claims 75-86 are drawn to kits comprising primers and probes of the same scope. Again, since the claims recite the

term "comprising", and the claims encompass nucleic acid primers and probes of any length. Also, the spacer region is not defined in terms of any particular nucleotide sequence or length. The claims also define the oligonucleotide in terms of its ability to hybridize specifically to a target. However, as discussed above, in the absence of a clear definition for the phrase "able to specifically hybridize," the language "specifically hybridize" has been interpreted broadly and is not considered to impart any particular structural or functional limitations onto the oligonucleotides.

Claims 70-72 are drawn to methods which require the use of primers "derived" from a spacer region between the large subunit and small subunit rRNA, the large subunit and the 5S subunit rRNA, or an RNA form thereof. The specification teaches that "rRNA gene spacer region derived" sequences refers to any probe that hybridizes to a spacer region. The conditions and specificity of hybridization are not defined. Accordingly, such sequences are given their broadest, most reasonable interpretation as encompassing spacer sequences which may include any number of nucleotide substitutions, deletions or additions. Thereby, the claimed primers are not considered to be defined in terms of a particular structure or length.

Nature of the Invention:

The claims are drawn to isolated nucleic acids comprising sequences of a spacer region between small and large subunit rRNA genes. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F. 3d 1316, 1330 (Fed Cir. 2001).

The Teachings in the Specification:

The specification discloses the spacer sequences between the 16S rRNA and 23S rRNA of 10 procaryotic microorganisms. The specification also exemplifies oligonucleotides from these spacer regions which can be used to distinguish between different species of the stated prokaryotic microorganism. For instance, the specification teaches oligonucleotides that can be used in a hybridization assay to distinguish between nucleic acids of *Neisseria meningitides* and nucleic acids of *Neisseria gonorrhoeae*. Accordingly, the specification has enabled nucleic acid probes and primers consisting of a sequence of a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, wherein the sequence comprises about 15 to about 100 contiguous nucleotides from a transcribed spacer region between the 16S and 23S rRNA genes of a prokaryotic microorganism, and wherein the probes or primers are species specific and do not includes sequences of a tRNA gene.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The specification teaches that the claimed nucleic acids are to be used as primers or probes to detect non-viral organisms and to specifically distinguish between different species of non-viral organisms. However, the prior art acknowledges the unpredictability of using nucleic acid sequences for the purposes of specifically detecting or distinguishing between species of organisms. Modification of even a single nucleotide within a sequence can significantly alter the hybridization specificity of a sequence. However, there is no specific disclosure provided in the specification as to particular nucleotides which are present in a representative number of internal

transcribed spacer regions of eukaryotic and prokaryotic organisms which are critical for maintaining the specificity of hybridization. It is thereby unpredictable as to how modifying the nucleic acid sequence of an internal transcribed spacer region, by adding, deleting or substitution nucleotides will effect the functional activities of the resulting nucleic acid sequence. There is also no specific disclosure provided in the specification of alternative regions which can be predictably used to develop probes or primers for the detection of any eukaryotic or prokaryotic organism. Thereby, it is also highly unpredictable as to what other regions outside of internal transcribed spacer regions could be used to generate probes or primers for the detection of any prokaryotic or eukaryotic organism.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably make and use nucleic acids probes and primers from the spacer region of eukaryotic organisms or from other regions of the genome of eukaryotic and prokaryotic organisms. While one could generate an infinitely large genus of nucleic acids from the internal transcribed spacer region of any eukaryotic or prokaryotic organism or from other regions of any eukaryotic or prokaryotic organism, analyze those sequences to determine which sequences are specific for a species and which sequences can be modified by adding nucleotides to the 5' and 3' terminus or by inserting, deleting or substituting any number and identity of nucleotides from within the sequence, and then assay each of the resulting nucleic acids to try to determine their biological activity and hybridization specificity, the outcome of such experimentation is highly unpredictable.

The specification itself acknowledges that particular probe and primer sequences can only be identified by "trial and error" experimentation. However, providing methods for searching for additional nucleic acids and trying to determine the function of the resulting nucleic acid is not equivalent to teaching how to make and use specific nucleic acids.

Working Examples:

Again, the specification teaches the sequences of the internal transcribed spacer region for 10 prokaryotic microorganisms and exemplifies primers and probes from these regions which are useful to detect these particular prokaryotic microorganisms. However, no working examples are provided of any primers or probes consisting of or comprising eukaryotic internal transcribed spacer sequences or any primers or probes comprising any prokaryotic or eukaryotic sequences from outside of the internal transcribed spacer region.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v*

Novo Nordisk 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches no members of the genus of primers and probes comprising spacer sequences from non-prokaryotic organisms, and teaches only 10 members of the genus of primers and probes comprising spacer sequences from prokaryotic organisms, whereas the claims encompass a significantly large genus of nucleic acids, in which the overall structural and functional properties of the nucleic acids are not defined. As set forth above, in view of the unpredictability in the art, extensive experimentation would be required to make and use additional nucleic acids because the specification does not provide sufficient guidance as to how to select the nucleotides which may flank these sequences, does not provide sufficient guidance as to how to modify these sequences by adding, substituting or deleting any number and identity of nucleotides, and does not provide sufficient guidance as to how to generate probes and primers from eukaryotic organisms which can be used for a practical purpose. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art, it would require undue experimentation for one of skill in the art to make and use the broadly claimed invention.

7. Claims 41-72 and 75-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41-72 and 75-86 are indefinite over the recitation of "RNA form." This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. It is unclear, for example, as to whether this phrase refers to a RNA molecule that is identical to the claimed nucleic acid molecule except that it contains a U in place of T, or whether this phrase refers to pre-processed or post-processed RNA variants of the nucleic acid molecule. In the absence of a clear definition for this term or a further characterization for this term in the claims, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Claims 43, 45, 47-49 are indefinite over the recitation of "able to hybridize specifically to a target." This phrase is not defined in the specification and there is no specific art recognized definition for this phrase. It is unclear as to what is intended to be meant by "specifically hybridize." For example, it is unclear as to whether such nucleic acids hybridize only to SEQ ID NO: 1 (and thereby are fully complementary to SEQ ID NO: 1) or if such nucleic acids also hybridize with variants of SEQ ID NO: 1 (e.g., variants having 99%, 98%, 95%, 90%, 70% etc identity with SEQ ID NO: 1). In the later case, there are no specific teachings provided in the specification to indicate the cut-off point at which the nucleic acid no longer specifically hybridizes to SEQ ID NO: 1. If the claimed nucleic acid is capable of hybridizing with a nucleic acid that differs from SEQ ID NO: 1 by even 1 nucleotide, then such nucleic acids are not truly specific for SEQ ID NO: 1. Because the phrase "specifically hybridizes" is not clearly defined in the specification or art, one cannot determine the meets and bounds of the claimed subject matter. The claims also do not set forth the condition under which the oligonucleotides

are "able" to hybridize. Accordingly, it is unclear as to how the recitation of "able to hybridize specifically to a target" is intended to further define the structure or function of the claimed oligonucleotides and the nucleic acid molecules comprising the oligonucleotides.

Claims 50-62 are indefinite over the recitation of "the nucleic acid sequences" because this phrase lacks proper antecedent basis. Further, the claims are indefinite over the recitation of "the hybrids." This phrase also lacks proper antecedent basis because the claims do not recite a clear step of forming hybrids, particularly between a probe and a complementary nucleic acid. While the claims recite a step of contacting nucleic acid sequences in general with a probe under conditions that allow for the formation of hybrids between a probe and an unstated complementary nucleic acid sequence, the claims do not recite that the nucleic acid sequences include complementary nucleic acid sequences and do not recite that a hybrid is formed between the probe and complementary nucleic acid sequences.

Claims 41-47 are indefinite for failing to recite a final process step which clearly relates back to the preamble. The claims are drawn to methods for detecting a plurality of microorganisms. However, the final process step is one for detecting "at least one microorganism" and thereby is inclusive of methods in which only a single microorganism is detected. Therefore, it is not clear as to whether the claims are intended to be limited to methods for detecting a plurality of microorganisms or to methods for detecting only one microorganism.

Claims 51, 54, 55, 57-62 and 70-72 are indefinite and vague over the recitation of "a large sub-unit and a small sub-unit" because it is not clear as to what this phrase is referring to – e.g., a large and small subunit of an rRNA gene or a large and small subunit of some other type of molecule.

Claim 54 is indefinite over the recitation of "the amplified product" because this phrase lacks proper antecedent basis. It is also unclear as to whether the phrase "is labeled" intends to infer an active process step or if this phrase indicates that it is an inherent property of the amplified product that it is labeled (e.g., all nucleic acids are essentially labeled since they can be detected).

Claim 55 is indefinite over the recitation of "the primer" because this phrase lacks proper antecedent basis since the claim previously refers to a primer set but not to a primer.

Claims 57-62 are indefinite because it is unclear as to whether the "a primer" is intended to refer to one of the primers of the primer set or to a different primer. In the later case, it is unclear as to the relationship between the primer and the method steps recited in the claims – i.e., the claims do not clarify how the amplification with the primer relates back to the method for the detection of a non-viral organism.

Claim 60 is indefinite over the recitation of "amplified products obtained from contacting" because this phrase lacks proper antecedent basis since the claim does not specifically recite a step of forming an amplified product and does not recite a contacting step.

Claims 63-66 are indefinite and vague because the claims do not set forth the essential method steps required to accomplish the objective of detecting an organism. The claims recite only a step of "using" a target, but do not recite how the target is used to accomplish the objective of detecting an organism.

Claim 66 is indefinite over the recitation of "the oligonucleotides" because this phrase lacks proper antecedent basis.

Claims 67-69 are indefinite over the recitation of "The method" because this phrase lacks proper antecedent basis since the claim does not previously refer to a method.

Claims 67-69 are indefinite over the recitations of "the nucleic acid sequences," and "the primer" because these phrases lack proper antecedent basis.

Claims 67-72 are vague and indefinite because the claims recite a step of comparing nucleic acid sequences and through the comparison step inferring the presence of a non-viral organism. However, the claims do not clarify how comparing nucleotide sequences to other unspecified nucleotide sequences allows for the detection of the presence of a non-viral organism.

Claims 70-72 are indefinite over the recitation of "the amplified nucleic acid sequence" because this phrase lacks proper antecedent basis.

Claims 75, 77-81 are indefinite over the recitation of "said primer" and "the primer" (claim 81) because this phrase lacks proper antecedent basis. While the claims previously refer to a set of primers, the claims do not previously refer to a primer.

Claims 75-86 are indefinite over the recitation of "the hybrids" because this phrase lacks proper antecedent basis.

Claims 80 and 84 are indefinite over the recitation of "the amplified products" because this phrase lacks proper antecedent basis. Further, the claims are indefinite because they recite a method step of "labeling the amplified product," however, the claims are directed to kits and not to methods. Thereby, it is unclear as to how this method step is intended to further limit the claims to kits.

Claims 81 and 86 are indefinite over the recitation of "immobilizing the primer" and "immobilizing the probe" because the claims are directed to a kit and not to a method. Thereby, it is unclear as to how the method step is intended to further limit the claims to kits.

Claim 85 is indefinite over the recitation of "the primer" because this phrase lacks proper antecedent basis since the claimed kit does not previously recite the inclusion of a primer.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 41-43, 46-63, 65-67, 69-70, 72, 75-76, 78-81, 83-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,536,638. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a genus of probes which is inclusive of the probes claimed in '638. Specifically, the claims of '638 are drawn to probes of the of N. gonorrhoeae transcribed spacer region and consist of the sequences of any one of SEQ ID NO: 1-8 and methods of detecting N. gonorrhoeae using said probes. The instant claims are drawn to probes which comprise sequences of the internal transcribed spacer region, and particularly the sequences of N. gonorrhoeae of SEQ ID NO: 1-8 and methods for detecting N. gonorrhoeae using said probes. Thereby, the broadly recited probes of the instant invention are inclusive of the probes claimed in '638. Furthermore, the claims of '638 do not recite packaging the probes specific for the spacer region in a kit. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made

to have packaged the probes of '638 in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect *N. gonorrhoeae*.

9. Claims 41-43, 46-63, 65-67, 69-70, 72, 75-76, 78-81, 83-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 5,945,282. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '282 are drawn to probes comprising a sequence from a transcribed spacer region between the 16S and 23S rRNA of a prokaryotic microorganism and methods for detecting prokaryotic microorganism using said probes. The claims of '282 do not recite kits containing said probes and additional reagents for the detection prokaryotic microorganisms. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the ITS probes and reagents for hybridization and amplification in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to specifically detect prokaryotic microorganisms.

10. Claims 41-43, 46-63, 65-67, 69-70, 72, 75-76, 78-81, 83-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-52 of U.S. Patent No. 6,277,577. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '577 both encompass probes comprising a sequence from a

transcribed spacer region between the 16S and 23S rRNA of a prokaryotic microorganism and methods for detecting prokaryotic microorganism using said probes.

11. Claims 41-43, 46-63, 65-67, 69-70, 72, 75-76, 78-81, 83-86 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,656,689. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '689 both encompass probes comprising a sequence from a transcribed spacer region between the 16S and 23S rRNA of a prokaryotic microorganism, methods for detecting prokaryotic microorganism using said probes, and kits containing said probes.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 41-50, 52, 53, and 63-65 are rejected under 35 U.S.C. 102(e) as being anticipated by Kohne (U.S. Patent 5,928,864; cited in the IDS).

The claims are drawn to probes and methods of detecting prokaryotic microorganisms using said probes wherein the probes comprise a sequence from the

transcribed spacer region between the 16S and 23S rRNA. It has been interpreted that the claims are inclusive of probes consisting of sequences of the tRNA genes since the tRNA genes are present within the internal transcribed spacer region. Further, in view of the comprising language, the present claims are inclusive of precursor rRNA sequences which include both spacer and rRNA sequences.

Kohne discloses and claims methods for detecting a microorganism present in a sample wherein the methods comprise contacting a sample nucleic acid with a probe and detecting hybridization of the probe to the sample nucleic acid as indicative of the presence of said microorganism. Kohne teaches that the probe consists of tRNA sequences which are specific for a particular organism (see, especially col. 3, 14 and 41-42) and states that a typical tRNA molecule is of a length of 75 to 85 bases (col. 2). Further, Kohne teaches that the probe may consist of precursor rRNA sequences (ps RNA) containing both spacer and rRNA sequences (see col. 19, 41-42 and 51). Kohne teaches that the probe is preferably a subsequence of the tRNA and ps RNA and that it may comprise 12 or more nucleotides and up to a thousand nucleotides (see col 19, and claim 1). The probe may be specific for a group of organisms, such as a genus or family, or may be specific for a particular species (see, e.g., claims 7 and 15). Kohne also teaches that tRNA and ps rRNA probes are generated by determining the tRNA or ps rRNA sequence of a target organism and the tRNA sequence or ps rRNA sequence of related organisms, comparing the sequences, and identifying unique sequences in order to design a probe specific for the target organism or group of organisms.

In particular, regarding claim 41, the claim recites the term "comprising" and thereby the nucleic acid molecule is not limited to one of any particular length. Further, the claim reads on the tRNA probes of Kohne does not require that the nucleic acid molecule comprise sequences of a spacer region, but rather only requires that the nucleic acid molecule comprises about the maximum number of nucleotides of any RNA form of a spacer region. The claim also reads on the ps rRNA probes of Kohne since these probes include spacer and rRNA sequences.

Regarding claim 42, Kohne teaches probes which comprise rRNA sequences (see, e.g., col. 35-36). Since claim 42 recites the claim language of "comprising" and defines the structure of the probe only in terms of the fact that it does not include tRNA genes, the rRNA probes of Kohne meet the limitation of the claims.

Regarding claims 43, 47-49, it is property of the probes of Kohne that they can hybridize non-specifically under low stringency conditions to target sequences lacking tRNA genes, as is encompassed by the claims.

Regarding claims 44, 45, 52, 64, Kohne teaches that the disclosed nucleic acids may be obtained from any eukaryotic organism (col. 1 and 4).

Regarding claims 46, 47, 53, 65, Kohne teaches that the disclosed nucleic acids may be obtained from any microorganism (col. 1 and 4).

Regarding claim 48, Kohne teaches that the nucleic acid molecule is a probe (see, e.g., col. 14).

Regarding claim 49, the recitation of the term "primer" does not distinguish the claimed nucleic acids over those of Kohne since the claimed nucleic acids and the

nucleic acids of Kohne have the same functional and structural properties and the nucleic acids of Kohne can serve as primers since they can be extended at the 3' end.

Regarding claims 50, 52, 53, and 63-65, Kohne teaches methods in which a target nucleic acid is contacted with a probe comprising sequences between the spacer region of rRNA under temperature and hybridization solution concentrations to allow for the formation of hybrids, wherein the formation of a hybrid infers the presence of an organism (see col. 14).

13. Claims 41, 43-49, 70-72 are rejected under 35 U.S.C. 102(b) as being anticipated by White (In: *PCR Protocols: A Guide to Methods and Applications*. Academic Press, New York. 1990. pages 315-322; cited in the IDS).

White teaches methods for specifically detecting eukaryotic microorganisms wherein the methods comprise amplifying nucleic acid sequences from a biological sample, determining the sequence of the amplified nucleic acids, and comparing the sequences of the amplified nucleic acids, wherein the primers are complementary to conserved sequences in the large and small subunit rRNA and amplify sequences between the large and small subunit rRNA genes and between the large subunit and 5S rRNA genes (see, e.g., pages 316 and 320-321 and Figure 1). White teaches that the large and small subunit rRNA contain regions of high levels of sequence conservation, as well as regions of sequence variability. White also teaches that primers may be obtained to the large and small subunit rRNA by identifying conserved sequences and teaches that such primers may be used to amplify sequences 3' and 5' to the large and small subunit rRNA, including sequences of the ITS region. In the method of White,

sequences of the amplification products are analyzed and compared. Since each of the method steps disclosed by White are the same as that set forth in the present claims, the method of White of amplifying, sequencing and comparing sequences is considered to accomplish the same objective set forth in the present claims of inferring the presence of a non-viral organism.

Regarding claims 41, 44 and 46, the amplification product formed by the method of White constitutes an isolated nucleic acid comprising a sequence of the maximum number of nucleotides between the large and small subunit rRNA genes or between the large subunit and 5S rRNA genes of a non-viral organism.

Regarding claims 43, 45, and 47, the amplification product formed by the method of White constitutes an isolated nucleic acid comprising an oligonucleotide of 15-100 contiguous nucleotides of a sequence of the maximum number of nucleotides between the large and small subunit rRNA genes or between the large subunit and 5S rRNA genes of a non-viral organism. It is a property of this nucleic acid that it can hybridize to a target that does not include tRNA genes.

Regarding claim 48, it is a property of the nucleic acid formed in the amplification method of White that this nucleic acid is a probe since the nucleic acid has the ability to hybridize to complementary nucleic acid sequences.

Regarding claim 49, the recitation of the term "primer" does not distinguish the claimed nucleic acids over those of White since the claimed nucleic acids and the nucleic acids of White have the same functional and structural properties and the nucleic acids of Kohne can serve as primers since they can be extended at the 3' end.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of Saiki (PNAS. 1989. 86: 6230-6234; cited in the IDS).

The teachings of Kohne are presented above. Kohne does not teach immobilization of probes onto solid supports.

However, Saiki (page 6234) teaches "reverse dot blot" methods for detecting nucleic acids in which probes are immobilized onto a solid support and then contacted with a target nucleic acid. Saiki teaches that this method offers the advantages of being able to reuse the filter containing the immobilized probes and provides a method in

which multiple probes with variations in the sequence can be employed in a single assay and the ability of these probes to hybridize with the target sequence can be readily ascertained because the location at which the probe is "dot-spotted" is known. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kohne so as to have immobilized the probes onto a solid support as taught by Saiki in order to have achieved the expected advantages expressly stated by Saiki of providing a detection assay which is economical, simple, robust and potentially automatable.

15. Claims 51, 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of White.

The teachings of Kohne are presented above. Kohne does not teach amplification of the target DNA by PCR prior to detection and particularly does not teach performing an amplification reaction using biotinylated primers or primers which hybridize to sequences of the 16S and 23S rRNA region.

However, White teaches methods for specifically detecting microorganisms in which primers complementary to conserved sequences in the large and small subunit rRNA region are used to amplify segments of the rRNA, including sequences of the internal transcribed spacer region. White teaches that the large and small subunit rRNA contain regions of high levels of sequence conservation, as well as regions of sequence variability. White teaches that primers may be obtained to the large and small subunit rRNA by identifying conserved sequences and teaches that such primers may be used

to amplify sequences 3' and 5' to the large and small subunit rRNA, including sequences of the ITS region.

In view of the teachings of White, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of detection of Kohne so as to have amplified the target nucleic acid prior to detection in order to have achieved the benefit of increasing the quantity of the target nucleic acid and thereby increasing the sensitivity of detection. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used primers complementary to conserved sequences of the 16S and 23S rRNA of prokaryotic microorganisms as the amplification primers in the modified method of Kohne in order to have provided an effective means for amplifying the ITS region containing tRNA sequences of prokaryotic microorganisms and thereby to have increased the quantity of the target prokaryotic nucleic acid and to have increased the sensitivity of detection of the target microorganism.

16. Claims 54, 55, and 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of White and further in view of Saiki.

The teachings of Kohne and White are presented above.

The combined references do not teach labeling the primers and thereby the amplification products with a biotinylated moiety.

However, Saiki discloses a nucleic acid detection method wherein the target nucleic acid is amplified using biotinylated primers in order to generate a labeled amplification product which is subsequently contacted with a filter containing dot-spotted

oligonucleotide probes. Hybridization of the labeled amplification product to the immobilized oligonucleotide probe is detected via the biotin moiety and is indicative of the presence of the target nucleic acid. In view of the teachings of Saiki, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the detection method of Kohne so as to have amplified the target nucleic acid prior to detection using a biotinylated primer in order to have achieved the benefit taught by Saiki of facilitating the detection of hybridization between the amplification product and the probe.

Regarding claim 62, Kohne and White do not teach immobilization of probes onto solid supports.

However, Saiki (page 6234) teaches "reverse dot blot" methods for detecting nucleic acids in which probes are immobilized onto a solid support and then contacted with a target nucleic acid. Saiki teaches that this method offers the advantages of being able to reuse the filter containing the immobilized probes and provides a method in which multiple probes with variations in the sequence can be employed in a single assay and the ability of these probes to hybridize with the target sequence can be readily ascertained because the location at which the probe is "dot-spotted" is known. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kohne so as to have immobilized the probes onto a solid support as taught by Saiki in order to have achieved the expected advantages expressly stated by Saiki of providing a detection assay which is economical, simple, robust and potentially automatable.

17. Claims 75-78, 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of the Stratagene Catalog (1988, page 38).

The teachings of Kohne are presented above. In particular, the method of Kohne requires the use of the reagents of an oligonucleotide probe which comprises an nucleic acid sequence consisting of sequences from the spacer region between rRNA genes, wherein said nucleic acid sequence can hybridize to a target that does not contain tRNA genes, hybridization buffer and reagents for detecting hybrids formed between said probe and target nucleic acid sequences. Kohne teaches the use of multiple oligonucleotide probes for the detection of multiple organisms. Regarding the limitation in claim 75 of a "set of primers," the probes of Kohne are considered to meet this limitation of the claims since the probes can be extended at the 3' end.

Kohne does not teach packaging the sets of oligonucleotides, hybridization buffer and detection reagents into a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the probes, hybridization buffer and detection reagents disclosed by

Kohne in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to detect the presence of a particular organisms.

18. Claim 79, 80, 81, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kohne in view of Saiki and further in view of the Stratagene Catalog.

The teachings of Kohne and Saiki are presented above. In particular, the method of Kohne in view of Saiki requires the use of the reagents of sets of oligonucleotide probes immobilized to a solid support, wherein the oligonucleotides comprise a nucleic acid sequence consisting of sequences from the spacer region between rRNA genes, wherein said nucleic acid sequences can hybridize to a target that does not contain tRNA genes and wherein said oligonucleotides may be labeled with a biotinylated moiety, hybridization buffer and reagents for detecting hybrids formed between said probe and target nucleic acid sequences. Kohne does not teach packaging these reagents in a kit.

However, reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid hybridization methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the immobilized probes, hybridization buffer and detection reagents disclosed by Kohne and Saiki in a kit for the expected benefits of convenience and cost-

effectiveness for practioners in the art wishing to detect the presence of a particular organisms.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
Art Unit 1634

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PRIMARY EXAMINER